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07/30/02 → 08/01/01

CLAIMS:

1. A 38-residue CRFR1 ligand peptide which binds to CRFR1 with an affinity substantially greater than it binds to CRFR2, which peptide has the following formula, or a nontoxic salt thereof:

Y₁-Pro-Pro-R₆-Ser-R₈-Asp-R₁₀-R₁₁-D-Phe-R₁₃-R₁₄-R₁₅-Arg-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-Gln-Glu-R₃₂-R₃₃-R₃₄-Arg-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-NH₂ wherein Y₁ is an acyl group having not more than 15 carbon atoms or is radioiodinated tyrosine; R₆ is Ile, Met or Nle; R₈ is Leu or Ile; R₁₀ is Leu or CML; R₁₁ is Thr or Ser; R₁₃ is His, Tyr or Glu; R₁₄ is CML or Leu; R₁₅ is CML or Leu; R₁₇ is Glu, CML, Asn or Lys; R₁₈ is Val, CML, Nle or Met; R₁₉ is CML, Leu or Ile; R₂₀ is Glu, D-Glu or His; R₂₁ is Nle, Leu, CML or Met; R₂₂ is Ala, D-Ala, Aib, Thr, Asp or Glu; R₂₃ is Arg or Lys; R₂₄ is Ala, Gln, Ile, Asn, CML or Aib; R₂₅ is Asp or Glu; R₂₆ is Gln, Asn or Lys; R₂₇ is CML, Glu, Gln or Leu; R₂₈ is Ala, Lys, Arg or Aib; R₂₉ is Gln, Aib or Glu; R₃₂ is Aib or an L- or D-isomer of a natural α-amino acid other than Cys; R₃₃ is Aib or an L- or D-isomer of Ser, Asn, Leu, Ala, CML or Ile; R₃₄ is Lys or Orn; R₃₆ is Lys, Orn, Arg, Har, CML or Leu; R₃₇ is CML, Leu, Nle or Tyr; R₃₈ is Nle, Met, CML or Leu; R₃₉ is Glu, Aib or Asp; R₄₀ is Ile, Aib, CML, Thr, Glu, Ala, Val, Leu, Nle, Phe, Nva, Gly or Gln; and R₄₁ is Ala, Aib, Ile, CML, Gly, Val, Leu, Nle, Phe, Nva or Gln; provided that a cyclizing bond may exist between Glu in position 31 and R₃₄ and provided further that D-2Nal or D-Leu may be substituted for D-Phe.

2. A peptide according to claim 1 having the formula:

(cyclo 31-34)Y₁-Pro-Pro-R₆-Ser-R₈-Asp-Leu-R₁₁-D-Phe-His-R₁₄-Leu-Arg-Glu-R₁₈-Leu-R₂₀-Nle-R₂₂-R₂₃-Ala-R₂₅-Gln-Leu-Ala-R₂₉-Gln-Glu-R₃₂-R₃₃-R₃₄-Arg-R₃₆-R₃₇-Nle-R₃₉-R₄₀-R₄₁-NH₂ wherein Y₁ is an acyl group having not more than 7 carbon atoms; R₂₀ is Glu or D-Glu; R₂₂ is Ala or Thr; R₂₉ is Gln or Glu; R₃₂ is His, Aib, Ala, Gly, Leu, Gln or Glu; R₃₆ is Lys or Leu; R₃₇ is Leu or CML; R₃₉ is Glu or Asp; R₄₀ is Ile, CML or Glu; and R₄₁ is Ile, Aib or Ala; with the remaining variables being as defined in claim 2.

3. A peptide according to claim 1 having the formula:

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-Leu-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Glu-Ile-Ile-NH₂, or
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(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Glu-Ile-CML-NH₂; or

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-Aib-Lys-Arg-Lys-Leu-Nle-Glu-Ile-CML-NH₂.

4. A peptide according to claim 1 having the formula:

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-Leu-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Glu-Ile-Ile-NH₂; or

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Glu-Ile-CML-NH₂; or

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-Aib-Lys-Arg-Lys-Leu-Nle-Glu-Ile-CML-NH₂.

Applicable

5. A CRF according to claim 1 having the formula:

Y₁-Pro-Pro-R₆-Ser-R₈-Asp-Leu-R₁₁-D-Phe-His-R₁₄-Leu-Arg-Glu-R₁₈-Leu-R₂₀-Nle-R₂₂-R₂₃-Ala-R₂₅-Gln-Leu-Ala-R₂₉-Gln-Glu-R₃₂-R₃₃-R₃₄-Arg-R₃₆-R₃₇-Nle-R₃₉-R₄₀-R₄₁-NH₂ wherein Y₁ is an acyl group having not more than 7 carbon atoms; R₂₀ is Glu or D-Glu; R₂₂ is Ala or Thr; R₂₃ is Arg or Lys; R₂₉ is Gln or Glu; R₃₁ is His, D-His, Aib or Ala; R₃₆ is Lys or Leu; R₃₇ is Leu or CML; R₃₉ is Glu or Asp; R₄₀ is Ile, CML or Glu; and R₄₁ is Ile, Aib or Ala; wherein the remaining variables are as defined in claim 2 and wherein the side chains of Glu³¹ and R₃₄ may be covalently connected.

6. A peptide according to claim 1 wherein R₁₈ is Val, R₂₂ is Ala, R₂₃ is Arg, R₂₄ is Ala, R₂₅ is Glu, R₂₈ is Ala, R₃₉ is Glu, and R₄₁ is Ile.

7. A peptide according to claim 1 having the following formula, or a nontoxic salt thereof:

(cyclo 31-34)Y₁-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-R₂₂-R₂₃-Ala-Glu-Gln-R₂₇-Ala-Gln-Gln-Glu-R₃₂-R₃₃-Lys-Arg-Lys-Leu-

23 = 611

Nle-Glu-R₂₀-Ile-NH₂ wherein R₂₂ is Ala or Thr; R₂₇ is Leu or CML; R₃₂ is His or Aib; R₃₃ is Ser or Aib; and R₄₀ is Ile or CML.

8. A peptide according to claim 1 having the formula:

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-Leu-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Glu-Ile-Ile-NH₂, or

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Glu-Ile-CML-NH₂; or

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-Aib-Lys-Arg-Lys-Leu-Nle-Glu-Ile-CML-NH₂.

3, 3, 8.

duplicate

9. A peptide according to claim 1 which is useful as a tracer that selectively bonds to CRFR1 wherein Y is radioiodinated D-Tyr or L-Tyr. *lack of antecedent.*

10. A 38-residue CRFR1 ligand peptide which binds to CRFR1 with an affinity substantially greater than it binds to CRFR2, which peptide has the formula Y₁-Pro-Pro-A-D-Xaa-B-Glu-Xaa_a-Xaa_b-Xaa_c-C-NH₂ wherein Y₁ is an acyl group having not more than 15 carbon atoms or is radioiodinated tyrosine; A is a sequence of 6 amino acid residues that is found between Pro in the 5-position and Phe in the 12-position of r/hCRF or the corresponding sequence of another peptide of the CRF family; D-Xaa is D-Phe, D-2Nal or D-Leu; B is a sequence of 18 amino acid residues that is found between Phe in the 12-position and Ala in position-31 of r/hCRF or the corresponding sequence of another peptide of the CRF family; Xaa_a is any L- or D-natural α -amino acid other than Cys or is Aib; Xaa_b is Aib or an L- or D-isomer of Ser, Asn, Leu, Ala, CML or Ile; Xaa_c is either Lys or Orn, the side chain of which may be linked in an amide cyclizing bond to that of Glu; and C is a sequence of the last 7 amino acid residues of the C-terminal portion of any peptide of the CRF family; provided that Nle or Leu may be substituted for Met in A, B and/or in C.